## DETAILED ACTION

This Action is in response to the communication filed on 9/8/2011.

The amendment filed 9/8/2011 is acknowledged and has been entered.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

### *Status of the Claims*

Claims 33-39, 41-43 49-53, 55 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/14/10.

Claims 30-32, 40, 44-48, 54, 56, 57-59 are examined herein, as they are drawn to the elected invention.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 is drawn to: the modified siRNA of claim 30 wherein the antisense strand **optionally comprises** an LNA at one or more of positions 2, 3, and 4 counting from the 3' end and does not comprise an LNA at any other position (Emphasis added).

Regarding claim 59, the phrase "optionally comprises" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-32, 40, 44, 54, 57, 58 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. 2004/0180351 (Giese).

It is noted that the elected species is a modified siRNA having a LNA at position 14of the sense strand, wherein each strand comprises 17-25 monomers. It is also noted that none of the claims included in this rejection are explicitly limited to having a LNA at position 14 of the sense strand. Searching the prior art, no references were found which taught the elected species (e.g., LNA at position 14); however, the instant reference does teach having a modified RNA nucleotide at position 14. Since it is clear that the reference applies as 102 art over non-elected species which are claimed, the reference is applied here as a 102 reference against the claimed (but non-elected) embodiments which it teaches.

Giese teaches a modified siRNA comprising a sense strand having a modified RNA nucleotide at position 14 (calculated from the 5'end), wherein each strand comprises 17-25 nucleotide monomers. Specifically, Geise teaches a siRNA comprising a sense and antisense strand that each comprises 21 nucleotide monomers and wherein sense strand comprises a modified RNA nucleotide (2'O-methyl) at position 14. For instance see Figures 10, 12 where "79A" is a sense strand of a siRNA molecule wherein all of the nucleotides are 2'O-methyl modified nucleotides. Thus Geise anticipates an siRNA 17-25 nucleotides in length and having a modified RNA nucleotide at position 14 of the sense strand, as well as a further comprising modified nucleotides at positions 8-13 and wherein the sugar moiety differs from ribose (i.e., ¶ [0082] of the specification indicates that the non-ribose sugar moiety can have a 2'O-methyl), and wherein the antisense strand does not have LNA at the 5'-end.

It is noted that amending the independent claim(s) to include the limitation that the modified RNA nucleotide is a LNA would obviate this rejection.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

1. Claims 30-32, 40, 44-48, 54, 56, 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braasch et al. (Biochem. 2003, cited by Applicant).

2. Braasch et al. teach siRNAs that can be 21 nucleotides in length which can comprise chemical modifications, including locked nucleic acids (LNA), in either the sense or antisense strands that impart increased potency, stability and/or pharmacokinetic properties (e.g., see

abstract, Fig. 7, etc.). At Figure 7, Braasch et al. teach a number of different specific siRNAs having one or more LNA modifications at various locations throughout the siRNA molecule, and explicitly teach a siRNA having a LNA at positions 8 and 13 from the 5'-end (e.g., see Fig. 7, siRNA identified as "L3 and "L5"). At Figure 7, Braasch et al. teach that the LNA has a structure that is encompassed by the structure of the beta-D-oxy-LNA shown in the specification as Scheme 2(2A) and Scheme 3(2A).

3. Braasch et al. do not specifically teach that the LNA modification is located at position 14 from the 5'-end of the sense stand of the siRNA molecule.

4. However, Braasch et al. demonstrate that LNA modifications can be placed throughout the sense and antisense strands of a siRNA molecule without diminishing efficacy. Furthermore, Braasch et al. specifically teaches,

> "These data suggest that LNA substitutions are well-tolerated and can lead to large increases in Tm values. However, to maximize the likelihood that potent inhibition of gene expression will be maintained, LNA substitutions should be kept to a minimum and should not infringe on the central region of the RNA. It is not difficult to meet these criteria since only modest numbers of LNA substitutions are necessary to significantly increase Tm."

Therefore, it would have been prima facie obvious to one of ordinary skill in the art, at the time of invention, that the siRNA oligonucleotide of Braasch et al. could be modified such that it comprised LNA at position 14 from the 5'-end of the sense strand, with a reasonable expectation of success.

See the Supreme Court decision in *KSR International CO. v. TELEFLEX INC.,* No. 04-1350 (U.S. Apr. 30, 2007). Also, at page 13, the Court stated, "If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would

recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." At page 15, the Court expressed, "The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patent. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way." At page 17, the Court expressed "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." (emphasis added)

Since the skills required to make the LNA modification at position 14 were within the technical grasp of one of ordinary skill in the art at the time of the invention, it would have been obvious to one of ordinary skill in the art to perform routine optimization using the known oligonucleotide chemical modification to arrive at the claimed siRNA. See *In re Aller*, 105 USPQ 233 at 235, which teaches that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and in the instant case, no evidence has been presented that the selection of position 14 for the LNA was other than routine, or that the products having LNA at position 14 has any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. Further, considering that Braasch et al. provides guidance which clearly indicates that LNA modification should not be in the central region of siRNA, there would have been motivation to place the

LNA near the end of the siRNA, and position 14 of a 21 nucleotide would be at a position expected to result in a functional siRNA, based on the fact that Braasch et al indicates that modification at position 13 results in a functional siRNA (e.g., see Figs. 7-8, etc.).

5. Claims 30-32, 40, 44-48, 54, 56, 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 2005/0261212 (McSwiggen et al.).

6. McSwiggen et al. teach siRNAs that can be 19 to 23 nucleotides in length which can comprise chemical modifications in either the sense or antisense strands that impart increased stability and/or nuclease resistance (e.g., see claims including claim 37-46). At paragraph 63 McSwiggen et al. teach that the siRNAs can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid nucleotides at the 5'-end, 3'-end, 5' and 3'-end, or any combination thereof. At paragraph 163 McSwiggen et al. teach that the locked nucleic acid nucleotides are 2', 4'-C methylene bicyclo nucleotide (and refer to WO 99/14226, Wengel et al. as an example (note: Wengel et al. is cited by Applicant). The 2', 4'-C methylene bicyclo nucleotide referred to by McSwiggen et al. is encompassed by the structure of the beta-D-oxy-LNA shown in the specification as Scheme 2(2A) and Scheme 3(2A).

7. McSwiggen et al. do not specifically teach that the LNA modification is located at position 14 from the 5'-end of the sense stand of the siRNA molecule.

8. However, McSwiggen et al. teach that functional siRNA can comprise LNA modification throughout the siRNA, including explicitly teaching that there can be "10 or more" modifications at the 5'-end, 3'-end, or both ends.

See the Supreme Court decision in *KSR International CO. v. TELEFLEX INC.,* No. 04-1350 (U.S. Apr. 30, 2007). Also, at page 13, the Court stated, "If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." At page 15, the Court expressed, "The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patent. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way." At page 17, the Court expressed "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." (emphasis added)

Since the skills required to make the LNA modification at position 14 were within the technical grasp of one of ordinary skill in the art at the time of the invention, it would have been obvious to one of ordinary skill in the art to perform routine optimization using the known oligonucleotide chemical modification to arrive at the claimed siRNA. See *In re Aller*, 105 USPQ 233 at 235, which teaches that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and in the instant case, no evidence has been presented that the selection of position 14 for the LNA was other than routine,

or that the products having LNA at position 14 has any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that Braasch does not teach that LNA can be placed throughout the sense and antisense strands without decreasing efficacy and that 3 of 4 siRNA having internal LNA were essentially inactive and that the reasons for the different efficacies is not obvious and that Braasch concludes that to maximize the likelihood that potent inhibition of gene expression will be maintained, LNA substitutions should not infringe on the central region of the RNA. Applicant contends that Braasch would discourage one from placing a modified RNA at position 14. Applicant acknowledges that McSwiggen suggests that LNA can be used at up to 10 positions from either the 5' or 3' end, but argues that McSwiggen does not disclose any examples of siRNA with LNA and that in view of Braasch, LNA should be excluded from the central region.

In response, it is noted that Braasch studied LNA modification of siRNA in depth, and provides specific guidance for creating functional LNA-modified siRNA. For example, Braasch teaches that to more closely investigate the effects of LNA substitutions of RNAi they evaluated duplexes consisting of one native RNA strand and one LNA-RNA strand and found that when one strand of inactive LNA-RNA duplex is paired with a native RNA strand, inhibition of gene expression is observed, indicating that the placement of LNA nucleotides on the individual strands was NOT responsible for the lack of inhibition by the duplex (e.g., see Figs 6, 9 and page

7974: ¶ bridging columns 1-2). Furthermore, when the experiments were extended, they observed significant inhibition of gene expression for all duplexes except the pairing of native sense strand RNA with antisense strand L3, and indicates that these data demonstrate that LNA substitution of just one strand is adequate to generate increased Tm values.

Thus one of ordinary skill in the art would understand that providing a dsRNA with one native strand and one LNA-RNA strand would have a high probability of being a functional siRNA molecule. Furthermore, considering that the only non-functional native RNA/LNA-RNA duplex found was one that had a LNA-RNA antisense strand, there would be a motivation and higher expectation of success to make a dsRNA wherein the sense strand of the duplex is an LNA-RNA and the antisense strand is native RNA.

Therefore, Applicant's arguments are not persuasive.

## *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is (571)272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/
Primary Examiner, Art Unit 1635